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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,479	05/10/2006	Steffen Goletz	GULDE-63	4918

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,479	GOLETZ ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-83 and 85-121* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-83,85-101 and 103-121* is/are rejected.

7)☒ Claim(s) *102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/3/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 3, 2008 has been entered.

2. Claims 79, 88, 96, 98, 113-116 have been amended.
Claims 117-121 have been added.

3. Claims 79-83 and 85-121 are under examination.

4. The following Office Action contains NEW GROUNDS of Rejection.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on October 3, 2008 has been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Rejections Maintained/ NEW GROUNDS of Rejection

Claim Objections

7. Claim 102 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

8. Claims 113 and 115 are objected to because of the following informalities: the claims depend upon a cancelled claim. For the purposes of this office action claim 113 is being interpreted as being dependent upon claim 87. Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 80, 88, 90, and 96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 80 and 90 are vague and indefinite for reciting the phrase "a combination of SEQ ID No. 33 and SEQ ID No. 35". It is not clear how the sequences are being combined to form a functional recognition molecule.

b. Claims 88 and 96 are vague and indefinite for reciting the phrase "at least one sequence of sequences" followed by a single SEQ ID No. It is not clear which sequences are referred to by the plural "sequences". For the purposes of this office action the phrase is being interpreted to be referring to the single sequence following the phrase.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The rejection of claims 85, 86, 93, 94, 104-107, and 109-112 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained. The rejection of claims 79-83, 87-92, 95-103, 108, and 113-116 is withdrawn upon further consideration by the examiner.

The response filed October 3, 2008 has been carefully considered but it deemed not to be persuasive. The response states that in essence, the Examiner is alleging lack of proof of use in prevention and treatment aspects. It is respectfully submitted that

in view of Dr. Danielczyk's declaration under §1.132 and the experimental evidence contained therein, this issue of is moot. For example, the studies outline the various uses of the recognition molecules of the present invention towards diagnostic, therapeutic, and/or preventive applications. Both in vitro and in vivo models were utilized (see response page 32). The declaration filed October 3, 2008 provides data allegedly supporting the treatment and prevention of cancer with the instant antibody (see entire declaration).

In response to these arguments, the declaration of Dr. Danielczyk provides data in which animals were injected with tumor cells and then the antibody of the invention (see figure 17). None of the experiments in the declaration, or in the instant specification, provide evidence to support prevention of the development of cancer by administering the antibody before the administration of the cancer cells, or by preventing the development of a tumor or predicting the development of a tumor. The experiments listed as the prevention model (see page 2 of the declaration and figure 17b) slowed tumor growth relative to control but did not prevent the development of a tumor. Thus, the data provided by the declaration and the instant specification support a method of treatment, reducing, or diagnosing a Muc1 associated tumor, but do not provide support for predicting, preventing, follow up or after care, or treatment of metastasis of a Muc 1 expressing tumor, nor treatment, reducing, or diagnosing a non-Muc1 associated tumor.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

13. Claims 88 and 96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recognition molecule which contains all 6 CDRs of an antibody, does not reasonably provide enablement for a recognition molecule comprising fewer than all 6 CDRs of an antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims recite a recognition molecule comprising one or more amino acid sequences, wherein at least one sequence of sequences SEQ ID NO: 1 is replaced by an equivalent canonical structure variant in accordance with SEQ ID NOs: 17 to 20; and/or at least one sequence of sequences SEQ ID NO: 3 is replaced by an equivalent canonical structure variant in accordance with SEQ ID NO: 21 and/or at least one sequence in accordance with SEQ ID NO: 7 is replaced by an equivalent canonical structure variant in accordance with SEQ ID NOs: 24 to 26; and/or at least one sequence of sequences SEQ ID NO: 11 is replaced by an equivalent canonical

structure variant in accordance with SEQ ID NO: 30; wherein said recognition molecule specifically binds to a glycosylated MUC1 tumor epitope. A recognition molecule comprising one or more amino acid sequences, wherein at least one sequence of sequences SEQ ID NO. 2 is replaced by an equivalent canonical structure variant in accordance with SEQ ID Nos. 13 to 16; and/or at least one sequence of sequences SEQ ID NO. 4 is replaced by an equivalent canonical structure variant in accordance with SEQ ID Nos. 22 or 23; and/or at least one sequence in accordance with SEQ ID NO. 8 is replaced by an equivalent canonical structure variant in accordance with SEQ ID Nos. 27 to 29; and/or at least one sequence of sequences SEQ ID NO. 12 is replaced by an equivalent canonical structure variant in accordance with SEQ ID No. 31; and wherein the recognition molecule specifically binds to a glycosylated MUC1 tumor epitope.

The specification teaches antibodies with 6 CDR regions that bind to MUC1. The specification does not teach antibodies having fewer than all 6 CDR regions.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which

maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol. 79, page 1979, as cited on the PTO-892 mailed June 27, 2007). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745, as cited on the PTO-892 mailed June 27, 2007) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). De Pascalis, et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084, as cited on the PTO-892 mailed June 27, 2007) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205, as cited on the PTO-892 mailed June 27, 2007) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428, as cited on the PTO-892 mailed June 27, 2007) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm et al (Molecular Immunology, 2007. Vol. 44, pages 1075-1084, as cited on the PTO-892 mailed June 27, 2007) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881, as cited on the PTO-892 mailed June 27, 2007) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of

residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162, as cited on the PTO-892 mailed June 27, 2007) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce a functional antibody comprising fewer than 6 CDR regions. The specification does not teach how to make an antibody that would bind MUC1 and comprise fewer than 6 CDR regions.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to make the claimed antibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the claimed antibody and absent working examples providing evidence which is reasonably predictive that the claimed antibodies are effective binding molecules, commensurate in scope with the claimed invention.

14. Claims 119 and 121 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The response filed October 3, 2008 has introduced NEW MATTER into the claims. Newly added claims 119 and 121 recite that the recognition molecule of base claims 87 and 95 is synthetic. The response pointed to the disclosure of the Examples to provide support for the new claims (see response page 30). The examples do not provide support for the term "synthetic". Instant claims 119 and 121 now recite limitations, which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such limitations recited in newly added claims 119 and 121, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C 112. Applicant is required to provide sufficient written support for the limitations recited in present claims 119 and 121 in the specification or claims, as-filed, or remove these limitations from the claims in response to this Office Action.

Claim Rejections - 35 USC § 101

15. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

16. The rejection of claims 79-83 and 85-101, 103-116, and newly added claims 117, 118, and 120 under 35 U.S.C. 101 as being directed to non-statutory subject matter is maintained.

The response filed October 3, 2008 has been carefully considered by the examiner but is deemed not to be persuasive. The response states that the claims convey to the skilled worker that the recognition molecules are polypeptides having the sequence set forth in the claims, wherein the structural (i.e., amino acid sequences) and the functional (i.e., capability to bind specifically to MUC-1 tumor epitope) aspects thereof are well- described in the originally-filed specification (see response page 31).

In response to this argument, while applicant's specification describes a recombinant recognition molecule or antibody, the claims as written do not distinguish from naturally occurring recognition molecules and are thus drawn to non-statutory subject matter. Amendment of the claims to recite an isolated recognition molecule would obviate this rejection.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Conclusion

17. Claims 79-83, 85-101, and 103-121 are rejected.

Claim 102 is objected to.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

//Sheela J Huff//
Primary Examiner, Art Unit 1643

Anne M. Gussow

December 10, 2008